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Uncatalyzed and Solvent-Free Multicomponent Process for the Synthesis of Biphenyl-2-carbonitrile Derivatives

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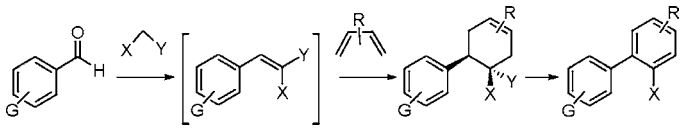
ABSTRACT



An innovative route to prepare a number of variously substituted new biphenyl derivatives is presented here. The protocol avoids the use of a catalyst, an organic solvent, and dry conditions.

Biphenyls represent a key structural motif in a large number of compounds used as pharmaceuticals, agrochemicals, dyes, chiral ligands for metal catalysts, liquid crystals, organic semiconductors, and materials for molecular recognition devices.[1] Furthermore, the biaryl subunit is present in an extensive range of natural products.[1]

The most widely employed method for their preparation involves a cross-coupling reaction of aryl halides, or their synthetic equivalent such as triflates, with aryl metal compounds.[2] In addition, progress has been recently made in the palladium-catalyzed direct arylation of simple arenes.[3]

Among all the possible organometallics, tin (Stille coupling),[4] boron derivatives (Suzuki−Miyaura coupling),[5] and to a lesser extent organozinc (Negishi coupling), organomagnesium (Kumada coupling), and organosilicon reagents (Hiyama) have been the most frequently used.[3] To promote these coupling reactions, various metal catalysts have been used and particular attention has been paid to palladium complexes.[3,6] The uncatalyzed synthesis of the biphenyl system has been scarcely investigated,[7] and solvent-free conditions (SolFC) have never been used.

Considering the importance of this class of compounds, the development of a green approach for their synthesis is desirable.

As a continuation of our studies on the use of water[8] and SolFC[9] in organic synthesis, we are currently involved in a project aimed at the definition of an innovative synthesis of

(1) Bringmann, G.; Gunther, C.; Schupp, O.; Tesler S. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Falk, H., Kirby, G. W., Moore, R. E., Eds.; Springer-Verlag: New York, 2001; Vol. 81, pp 1−293.

(2) (a) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; De Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004. (b) Cross-Coupling Reactions. A Practical Guide. In *Top. Curr. Chem.*; Miyaura, N., Ed.; Springer-Verlag: Berlin, 2002; Vol. 219.

(3) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253−1264.

(4) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1−652.

(5) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359−1469.

(6) Tsuji, J. *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*; Wiley: Chichester, U.K., 2004.

(7) Becht, J.-M.; Gissot, A.; Wagner, A.; Miosjkowki, C. *Chem.−Eur. J.* **2003**, *9*, 3209−3215.

(8) As representative examples, see: (a) Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2004**, *67*, 2315−2321. (b) Fringuelli, F.; Pizzo, F.; Tortoioli, S.; Vaccaro, L. *Org. Lett.* **2005**, *7*, 4411−4414 and literature cited therein.

(9) As representative examples, see: (a) Fringuelli, F.; Pizzo, F.; Vittoriani, C.; Vaccaro, L. *Chem. Commun.* **2004**, 2756−2757. (b) Fringuelli, F.; Girotti, R.; Pizzo, F.; Vaccaro, L. *Adv. Synth. Catal.* **2006**, *348*, 297−300 and literature cited therein.

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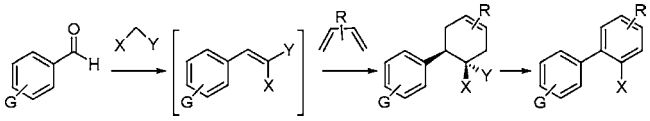
2-substituted biphenyls under SolFC, via a metal-free multicomponent strategy, which starting from an aryl aldehyde is based on the construction of the second aryl ring by a (1) Knoevenagel reaction, (2) Diels−Alder cycloaddition, and (3) final aromatization process (Scheme 1).

Scheme 1. Multicomponent Approach under SolFC to the Biphenyl System

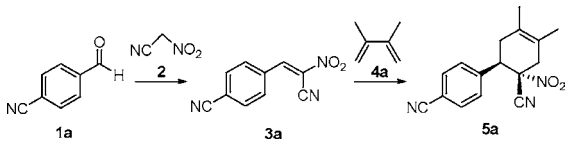


To our knowledge, this synthetic approach has been realized in organic solvent and only for the preparation of 4′-methyl-1,1′-biphenyl-2-carbonitrile, but the yield was unsatisfactory.[10] We maintain that this approach could furnish under SolFC a valid synthetic tool for the preparation of 1,1′-biphenyl-2-carbonitriles.

In this communication, we report the synthesis of biphenyl-2-carbonitrile derivatives **6a**−**o** by using aryl aldehydes **1a**−**k**,**o**, nitroacetonitrile **2**, and the 1,3-butadienes **4a**−**d**. This class of biphenyls is an important target: they are little known and commonly prepared by Suzuki−Miyaura coupling.[11]

We have initially verified the feasibility of the process by preparing 4,5-dimethyl-1,1′-biphenyl-2,4′-dicarbonitrile (**6a**), studying (a) the preparation of cycloadduct **5a** (Table 1) and then (b) its aromatization (Scheme 2).

Table 1. Optimization of the Synthesis of the Intermediate **5a** at 30 °C

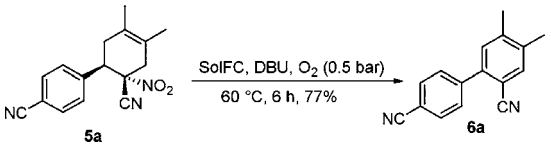


entry	reaction medium	reactants	time (h)	product	yield (%)[a]
1	water	**1a**, **2**	12	–	–
2	SolFC	**1a**, **2**	3	**3a**	75
3	water	**3a**, **4a**	10	**5a**	84
4	SolFC	**3a**, **4a**	10	**5a**	90
5	water	**1a**, **2**, **4a**	12	**5a**	72
6	SolFC	**1a**, **2**, **4a**	10	**5a**	85

[a] Isolated yield.

To optimize the synthesis of **5a**, we have used two approaches, one based on a step-by-step process (Table 1, entries 1−4) and the other on a multicomponent procedure performed in water or under SolFC (Table 1, entries 5 and 6). In the latter case, the result obtained was excellent; in fact, when the heterogeneous mixture of **1a**, **2**, and **4a** under SolFC was left under vigorous stirring at room temperature for 10 h, cycloadduct **5a** was isolated in 85% yield (Table 1, entry 6). All the experiments have been performed by using **1a**:**2**:**4a** 1:1.5:2.0 molar ratios.

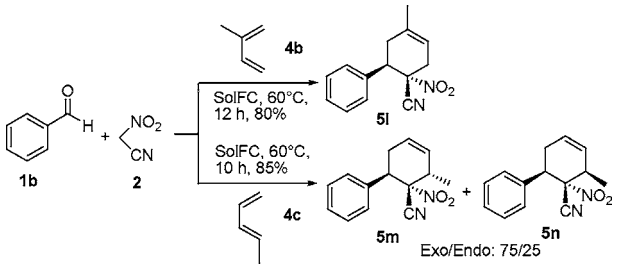
Scheme 2. Aromatization Process of Cycloadduct **5a**



To convert **5a** to biphenyl **6a**, we have tried many procedures, always obtaining unsatisfactory results. We have found that when **5a** was treated with 2.0 molar equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) under SolFC in the presence of O_2 (0.5 bar) at 60 °C for 0.5 h, 4,5-dimethyl-1,1′-biphenyl-2,4′-dicarbonitrile (**6a**) was isolated in a satisfactory 77% yield (Scheme 2).

The study was then extended to a variety of aldehydes **1b**−**k** and to 1,3-dienes **4a**−**c** (Table 2 and Scheme 3).

Scheme 3. Multicomponent Processes on **1b** by Using Isoprene (**4b**) and (*E*)-Piperylene (**4c**)



The multicomponent reaction among **1b**−**f**,**h**,**i**,**k**, **2**, and **4a** allowed at 30−60 °C in 5−20 h the corresponding cycloadducts **5b**−**f**,**h**,**i**,**k** to be isolated (Table 2, entries 1−5, 7, 8, and 10). In the case of electron-rich aldehydes **1g** and **1j**, the Knoevenagel condensation was performed at 30 °C, and to complete the Diels−Alder cycloaddition step in reasonable time (3 h), the temperature was raised to 120 °C (Table 2, entries 6 and 9). In all cases, the yields were excellent.[12]

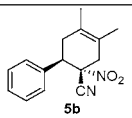
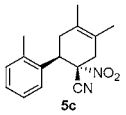
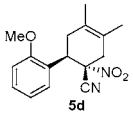
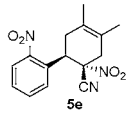
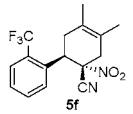
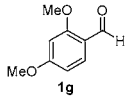
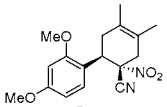
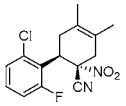
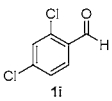
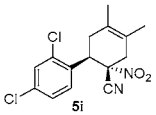
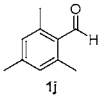
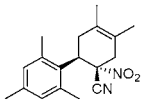
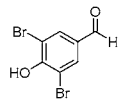
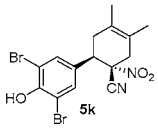
In addition, the reactions among **1b**, **2**, and isoprene (**4b**) or (*E*)-piperylene (**4c**) were also performed to evaluate the regio- and stereoselectivity of the process (Scheme 3). In the first case, para adduct **5l** was exclusively formed and isolated in 80% yield, whereas with **4c** the exo/endo adducts **5m**/**5n** were formed in a 75:25 ratio and isolated in 85% yield.

The aromatization of adducts **5b**−**n** was performed at 60 °C, generally in the presence of 2.0 molar equiv of DBU, under an O_2 atmosphere (0.5 bar) and SolFC. Biphenyl-2-

(10) Noda, Y.; Akiba, Y.; Kashima, M. *Synth. Commun.* **1996**, *26*, 4633−4639.

(11) (a) Zapf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4153−4155. (b) Yamada, Y. M. A.; Takeda, K.; Takahashi, H.; Ikegami, S. *Org. Lett.* **2002**, *4*, 3371−3374. (c) Tewari, A.; Hein, M.; Zapf, A.; Beller, M. *Synthesis* **2004**, 935−941. (d) Wang, G. T. et al. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 153−158.

Table 2. Multicomponent Synthesis of **5b**−**k** Using **1b**−**k**, **2**, and **4a** under SolFC

entry	aldehyde	temp (°C)	time (h)	adduct	yield (%)[a]
1	 **1b**	60	5	 **5b**	86
2	 **1c**	60	6	 **5c**	85
3	 **1d**	60	20	 **5d**	88
4	 **1e**	30	12	 **5e**	78
5	 **1f**	30	12	 **5f**	77
6	 **1g**	30 and 120	12 3	 **5g**	80
7	 **1h**	30	12	 **5h**	82
8	 **1i**	60	6	 **5i**	84
9	 **1j**	30 and 120	12 3	 **5j**	78
10	 **1k**	30	15	 **5k**	75

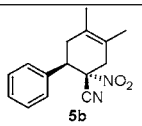
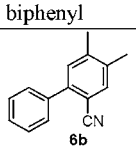
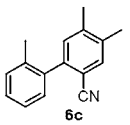
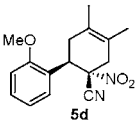
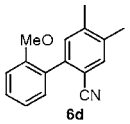
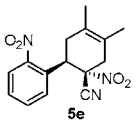
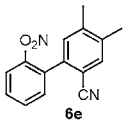
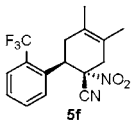
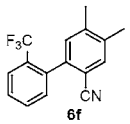
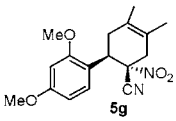
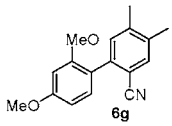
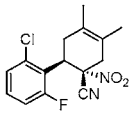
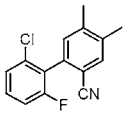
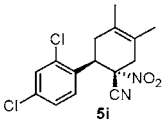
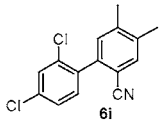
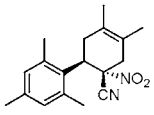
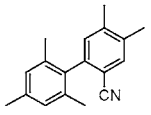
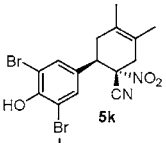
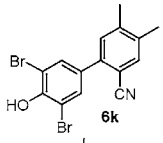
[a] Yield of isolated pure product.

carbonitriles **6b**−**n** were isolated in 0.5−7 h in satisfactory to excellent yields (Table 3).[13]

We have also prepared the 4′-methyl-1,1′-biphenyl-2-carbonitrile (**6o**) that is the precursor of angiostein II antagonists (Scheme 4).[11,14]

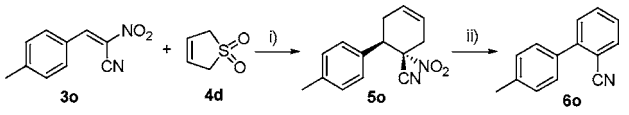
In this case, due to the significant tendency of benzylidene **3o** to give the retro Knoevenagel reaction at 110 °C, even in the presence of traces of water, the synthesis of **5o** was accomplished in a two-step procedure. After the completion of the condensation of *p*-methyl-benzaldehyde (**1o**) with **2** under SolFC (30 °C, 4 h), the resulting solid benzylidene **3o** was washed with water, rigorously dried under a vacuum, and then treated with sulfone **4d** at 110 °C for 12 h. The corresponding cycloadduct **5o** was obtained in 75% yield after silica gel column chromatography. The final aromatization furnished the desired 4′-methyl-1,1′-biphenyl-2-carbonitrile (**6o**) in 65% yield.

Table 3. Multicomponent Synthesis of **6b**−**n** under SolFC at 60 °C

entry	adduct	(h)	biphenyl	yield (%)[a]
1	 **5b**	3	 **6b**	75
2	 **5c**	6	 **6c**	57
3	 **5d**	3	 **6d**	60
4	 **5e**	6	 **6e**	57
5	 **5f**	2.5	 **6f**	70
6	 **5g**	5	 **6g**	45
7	 **5h**	2	 **6h**	70
8	 **5i**	5	 **6i**	70
9	 **5j**	3	 **6j**	62
10	 **5k**	7	 **6k**	80[b]
11	**5l**	4	**6l**	70
12	**5m/5n**	5	**6m/6n** [c]	65[d]

[a] Yield of isolated pure product. [b] 4.0 molar equiv of DBU. [c] **6m**/**6n** 57:43. **6m**: X = CN. **6n**: X = NO_2. [d] Overall yield for **6m**/**6n**

Scheme 4. Multicomponent Synthesis of 4′-Methyl-1,1′-biphenyl-2-carbonitrile (**6o**)



i) SolFC, 110 °C, 12 h, 75%; ii) DBU, O_2 (0.5 bar), 60 °C, 6 h, 65%

Working on a typical laboratory scale (1−2 mmol) and with equimolar amounts of reagents, magnetic stirring was not sufficient to ensure their necessary mixing, allowing a maximum 80% conversion. Therefore, the use of oversto-ichiometric amounts of nitroacetonitrile (**2**) and diene **4** was necessary to complete the reactions. Consequently, although the chemical efficiency of the process has been improved, its "greenness" has been lowered.

We have therefore investigated the possibility of improving the environmental efficiency of this process.

We have planned to (a) operate on a large scale that would enable the use of the more efficient mechanical stirrer, allowing operation with equimolar amounts of **2** and **4**, (b) perform the aromatization of cycloadducts **5** in the same pot on the crude products, and (c) isolate the pure biphenyls **6** by recrystallization to reduce the use of costly organic solvents.

Finally, 4-cyano-benzaldehyde (**1a**) (40 mmol) was charged in a metallic reactor equipped with a mechanical stirrer, and at 30 °C, nitroacetonitrile (**2**) (40 mmol) and diene **4a** (40 mmol) were subsequently added. After 10 h, the formation of cycloadduct **5a** was complete and DBU (80 mmol) was added in situ. The reactor was then sealed and left under mechanical stirring for 12 h at 30 °C under an O_2 atmosphere (0.5 bar). The final biphenyl **6a** was isolated as a pure compound after filtration of the reaction mixture through a silica gel pad (sample/silica gel, 1:1 ratio) and recrystallization from acetone, in a satisfactory 72% overall yield (see Supporting Information).

In conclusion, the approach to biphenyl systems presented herein avoids the use of a catalyst, an organic solvent, and dry conditions and makes the purification of the final products very simple. This protocol represents a promising green route to this class of compounds.

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Supporting Information Available: General experimental procedures and characterization data (^{1}H NMR, ^{13}C NMR, IR, R_f, mp, GC-MS analyses) for all compounds, copies of ^{1}H NMR and ^{13}C NMR for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) **General Procedure for the Preparation of Diels−Alder Adducts.** A screw-capped vial equipped with a magnetic stirrer was charged with the aldehydes **1a**−**k**, nitroacetonitrile **2** (1.5 molar equiv), and dienes **4a**−**c** (2.0 molar equiv). The resulting mixture was left under magnetic stirring for the time and at the temperatures reported in Tables 1 and 2 and in Scheme 3. Cycloadducts **5a**−**n** were isolated after silica gel column chromatography of the final mixture.

(13) **General Procedure for the Preparation of Biphenyls 6a−o.** A screw-capped vial equipped with a magnetic stirrer was charged with cycloadducts **5a**−**o** and DBU (2.0 molar equiv). The resulting mixture was left under O_2 (0.5 bar) under magnetic stirring at 60 °C for the time reported in Table 3 and Schemes 2 and 4. Biphenyls **6a**−**o** were isolated after silica gel column chromatography of the final mixture.

(14) Yamada, Y. M. A.; Takeda, K.; Takahashi, H.; Ikegami, S. *Org. Lett.* **2002**, *4*, 3371−3374 and literature cited therein.